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Rare 2-Substituted Purine Nucleosides

Annual Report

October 18, 1986 to October 17, 1987

October 1987

Vasu Nair

Supported by

U. S. Army Medical Research and Development Command
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-86-C-6001

The University of Iowa
Iowa City, Iowa 52242

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19. ABSTRACT (Continue on reverse if necessary and identify by block number)

This project is concerned with the synthesis of rare 2-substituted purine nucleosides with therapeutic potential against RNA viruses. In the second year of the contract, eleven rare 2-substituted purine nucleosides were synthesized, purified, fully characterized, and submitted to the Department of Antiviral Studies. Antiviral screening data have been received on a few of the compounds submitted and there are some very interesting and positive results. One compound (2-acetonylinosine, AVS-002159) has been found to have very high activity (TI >1000) against the SF virus. Another compound (2-vinylinosine, AVS-002716) has been found to have broad spectrum activity against a number of RNA viruses. Two other compounds (AVS-002883 and AVS-002884) have shown some activity against the RVF virus, and still another (AVS-002352) has shown activity against the YF virus. Five publications have appeared in 1987 on this work.

Keywords: Rift Valley Fever Virus; yellow fever virus;

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2. Name of Contractor: University of Iowa, Iowa City, Iowa 52242

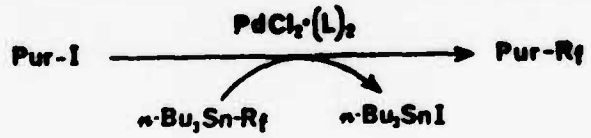
3. Name of Principal Investigator: Vasu Nair
Professor of Chemistry
Phone: (319) 335-1364

4. Reporting Period: October 18, 1986 to October 17, 1987

5. Description of Work in Progress:

In the second year of this contract, our goals were to utilize the procedures previously developed to synthesize a number of target molecules. A total of nine rare C-2 functionalized nucleosides (target compounds) were submitted to the Department of Antiviral Studies for biological evaluation between October 18, 1986 and October 17, 1987. In addition, two intermediates were submitted during this period. A description of the synthetic work done during this period, compounds submitted, biological test data, publications, personnel supported, and an executive summary are given in the pages following.

The starting point of our work during the second year of the contract was the synthesis of the 2-vinyl compounds 1 and 2. The rationale for the choice of these compounds as the starting point was that, in addition to being target molecules, they would also be key precursors for the synthesis of a variety of rare functionalized alkylated purine nucleosides. The general methodology for the introduction of carbon-carbon bonding at the 2-position of the hypoxanthine or purine ring systems developed in our laboratory under this contract is summarized in Scheme 1. The conversion apparently involves oxidative insertion of palladium into the carbon iodine bond of the iodopurine followed by coupling of the derived Pd(II) complex with the appropriate organostannane, trans-cis isomerization, and reductive elimination to give the coupled product with regeneration of the Pd(0). Only catalytic amounts of palladium are required for this reaction.

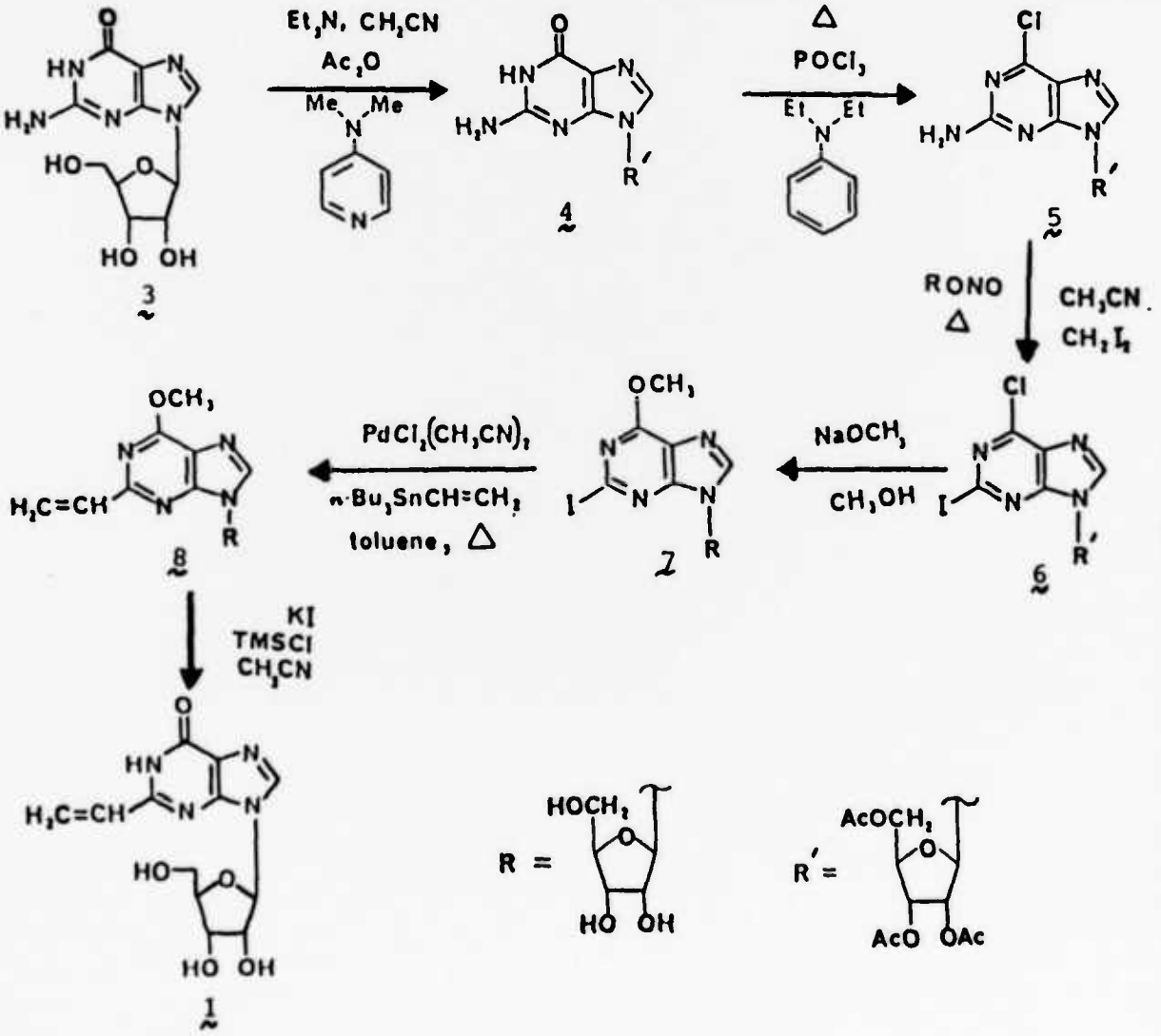


R_f = functionalized alkyl group

Scheme 1

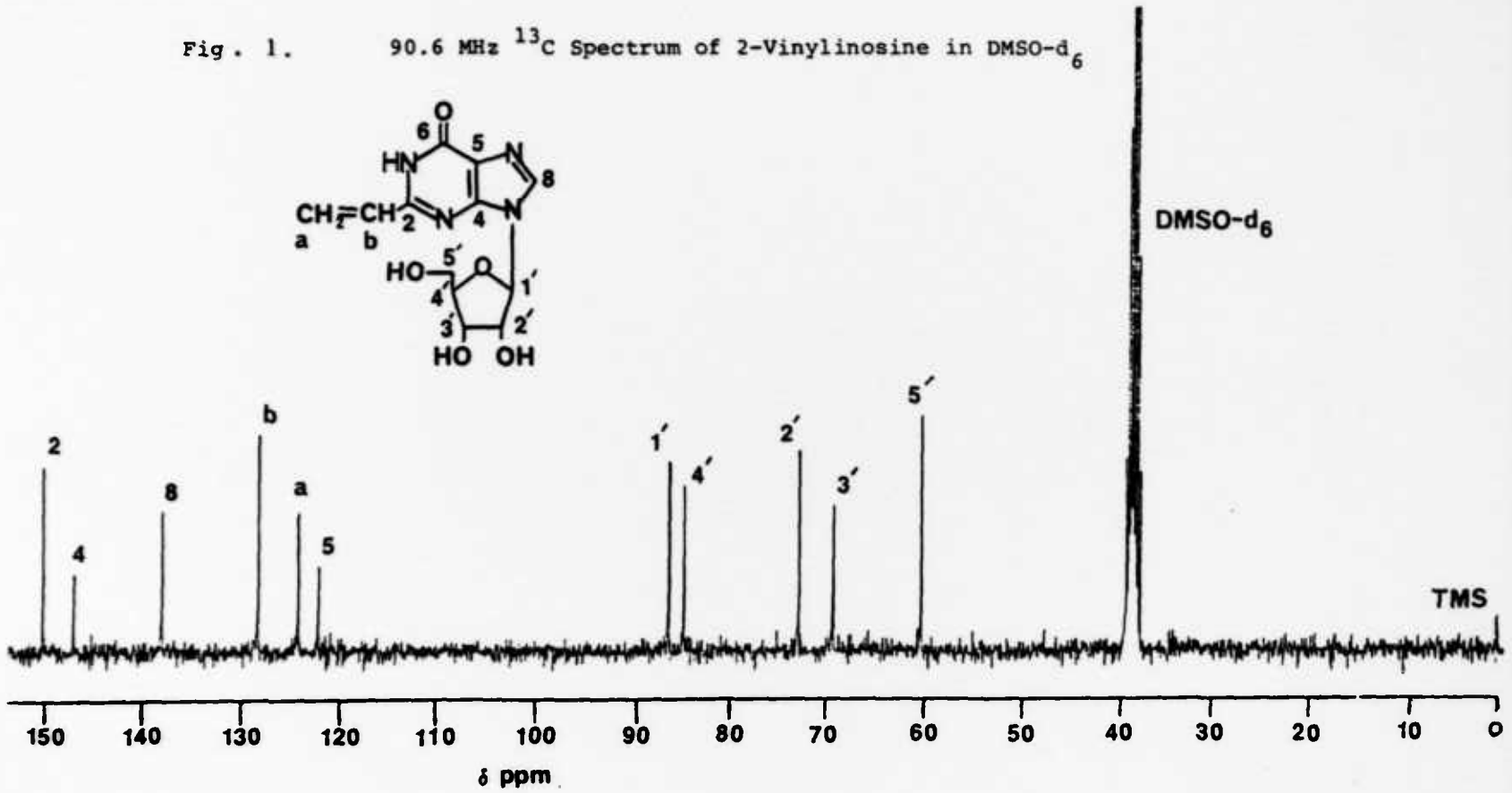
The synthesis of 2-vinylinosine (1) commenced with guanosine (3) which was converted in two steps with the reagents shown to the 2-amino-6-chloropurine nucleoside (5) in 83% overall yield. Reaction of compound 5 with n-pentyl nitrite and diiodomethane in refluxing acetonitrile gave the 6-chloro-2-iodopurine nucleoside 6 in 71% yield. In the next step, this molecule was modified in preparation for the introduction of functionalized

alkylation at the 2-position. Thus it was treated with sodium methoxide in methanol. The 6-chloro group was replaced with methoxide to produce the masked base and the protecting acetyl groups on the carbohydrate moiety were cleaved. The product, nucleoside 7 (76%), was now properly constituted for the palladium-catalyzed cross-coupling reaction. Thus, reaction of 7 with tri-n-butylvinylstannane in the presence of palladium chloride gave 8 in > 80% yield. Deprotection of 8 with trimethylsilyl iodide in acetonitrile resulted in cleavage of the methyl group to give the target molecule 1 in about 50 % yield after appropriate work up and purification (Scheme 2). Our procedure for masking the hypoxanthine base in this way will find wide application in purine nucleoside chemistry. Compound 1 was purified by high performance liquid chromatography (three passes) on Amberlite XAD-4 resin with ethanol-water as the eluting solvent. Complete characterization was carried out by UV, FTIR, high-field ^{1}H and ^{13}C NMR spectroscopy, and elemental analysis. The high-field ^{13}C NMR spectrum is enclosed (Fig. 1).

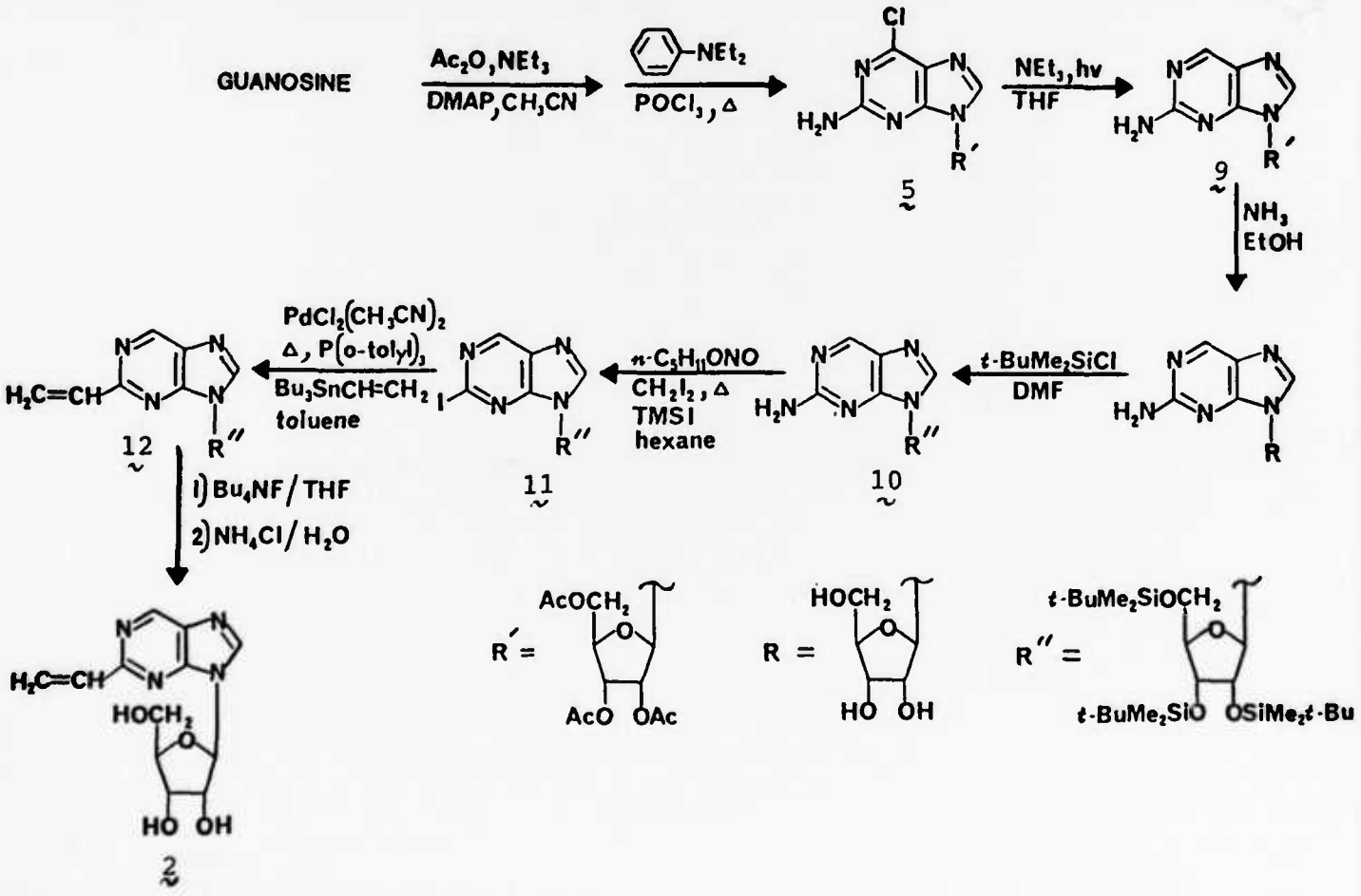


Scheme 2

Fig. 1. 90.6 MHz ^{13}C Spectrum of 2-Vinylinosine in DMSO-d_6

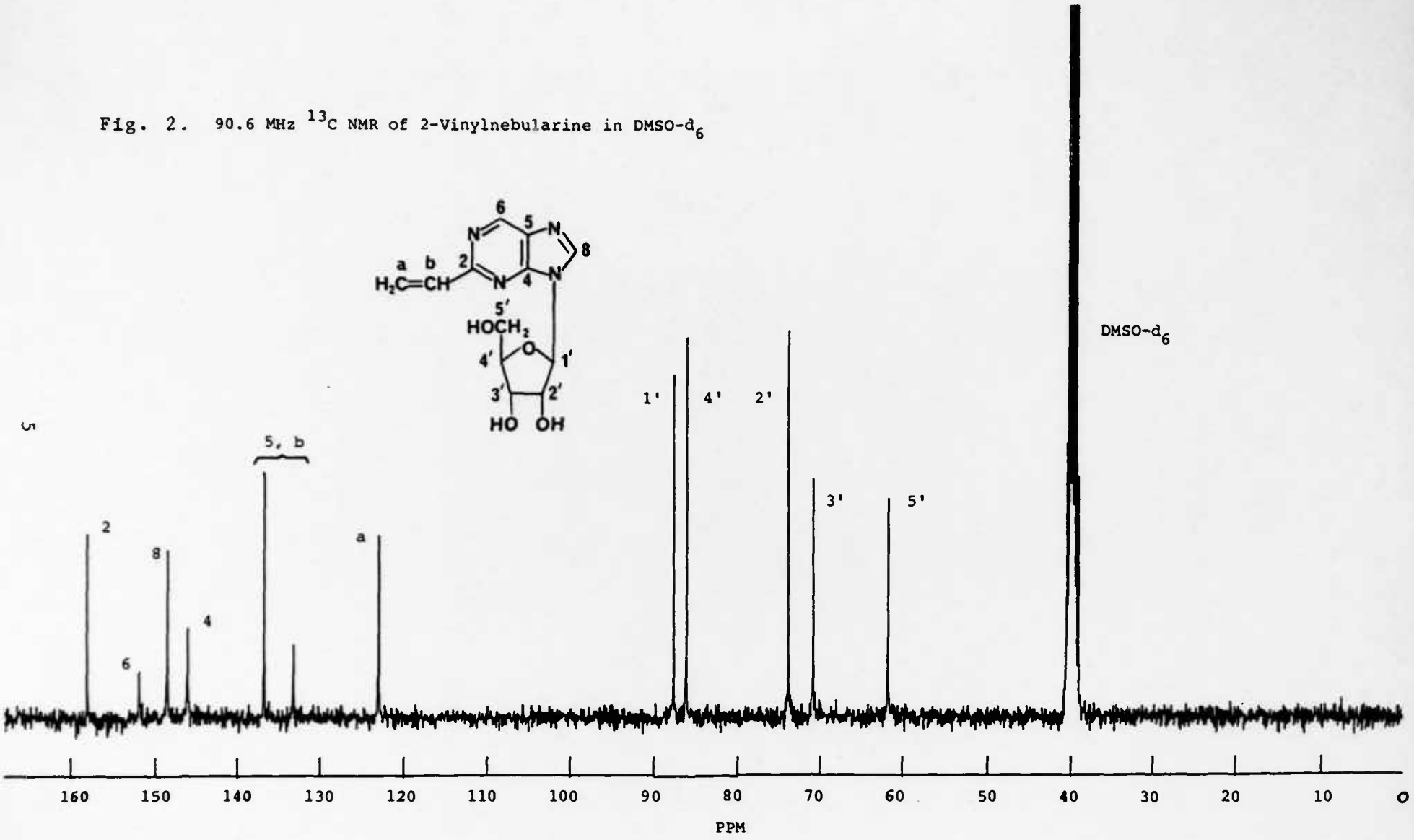


Compound 2 was synthesized using the sequence of reactions shown in Scheme 3. The starting material for the synthesis was the 6-chloropurine nucleoside 5, prepared from guanosine in 83% yield as described above. In order to obtain entry into 2-substituted purine nucleosides, it was necessary to remove the 6-chloro group. This was done by a photoinduced reductive dehalogenation reaction with triethylamine in tetrahydrofuran as solvent. This photochemical dehalogenation is a new methodology in nucleoside chemistry and was developed in this project. It will find wide applicability in the nucleoside area. Attempted radical iodination of the 2-aminopurine 9 gave poor yields of the 2-iodinated product. However, when the protecting group was changed from acetate to hindered silyl group, through deprotection followed by silylation, then the radical iodination reaction proceeded in much higher yields to give 11. Reaction of 11 with tri-n-butylvinylstannane under palladium catalysis gave the 2-vinylpurine nucleoside 12 which was deprotected with tetrabutylammonium fluoride to the target molecule 2. The overall yield starting from guanosine was 12%. The crude product was purified by flash chromatography followed by HPLC and fully characterized as described above for 1. The high-field ^{13}C NMR spectrum is shown in Fig. 2.

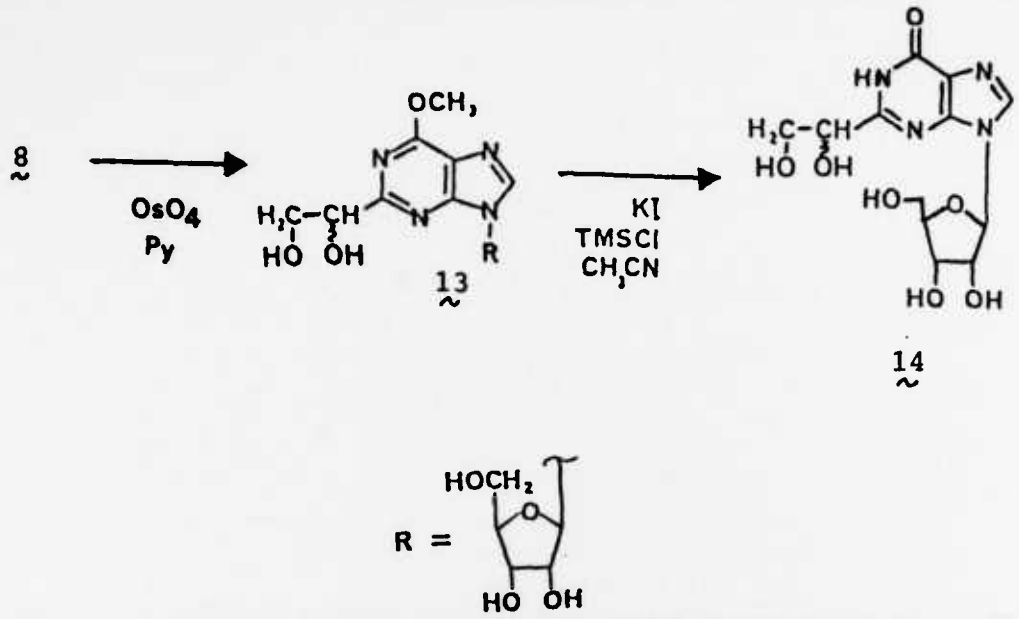


Scheme 3

Fig. 2. 90.6 MHz ^{13}C NMR of 2-Vinylnebularine in DMSO-d_6

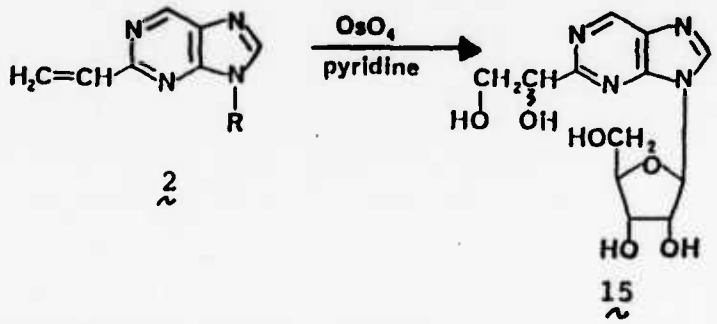


Hydroxylation of compound 8 with osmium tetroxide gave the 1,2-dihydroxyethyl compound 13 in 55 % yield. Deprotection of 13 with trimethylsilyl iodide in acetonitrile gave 14 in 50 % yield (Scheme 4). This target molecule was purified by HPLC on Amberlite XAD-4 resin. It was fully characterized by spectral methods and elemental analysis. The high-field ^{13}C NMR spectrum is enclosed (Fig. 3).



Scheme 4

Hydroxylation of compound 2 with osmium tetroxide followed by appropriate work-up and purification gave the target molecule 15 (Scheme 5). It was fully characterized by spectral methods and elemental analysis. The high-field ^{13}C NMR spectrum is shown in Fig. 4.



Scheme 5

Another target molecule synthesized and submitted was the 2-acetonylnebularine 17. The immediate precursor for 17 was the silylated 2-iodopurine nucleoside 11. When this compound was heated in toluene in the presence of palladium chloride, tri-o-tolylphosphine, tri-n-butyltin methoxide, and isopropenyl acetate, good yields of the expected 2-acetonyl

Fig . 3. 90.6 MHz ^{13}C Spectrum of 2-(1,2-Dihydroxyethyl)inosine in DMSO-d_6

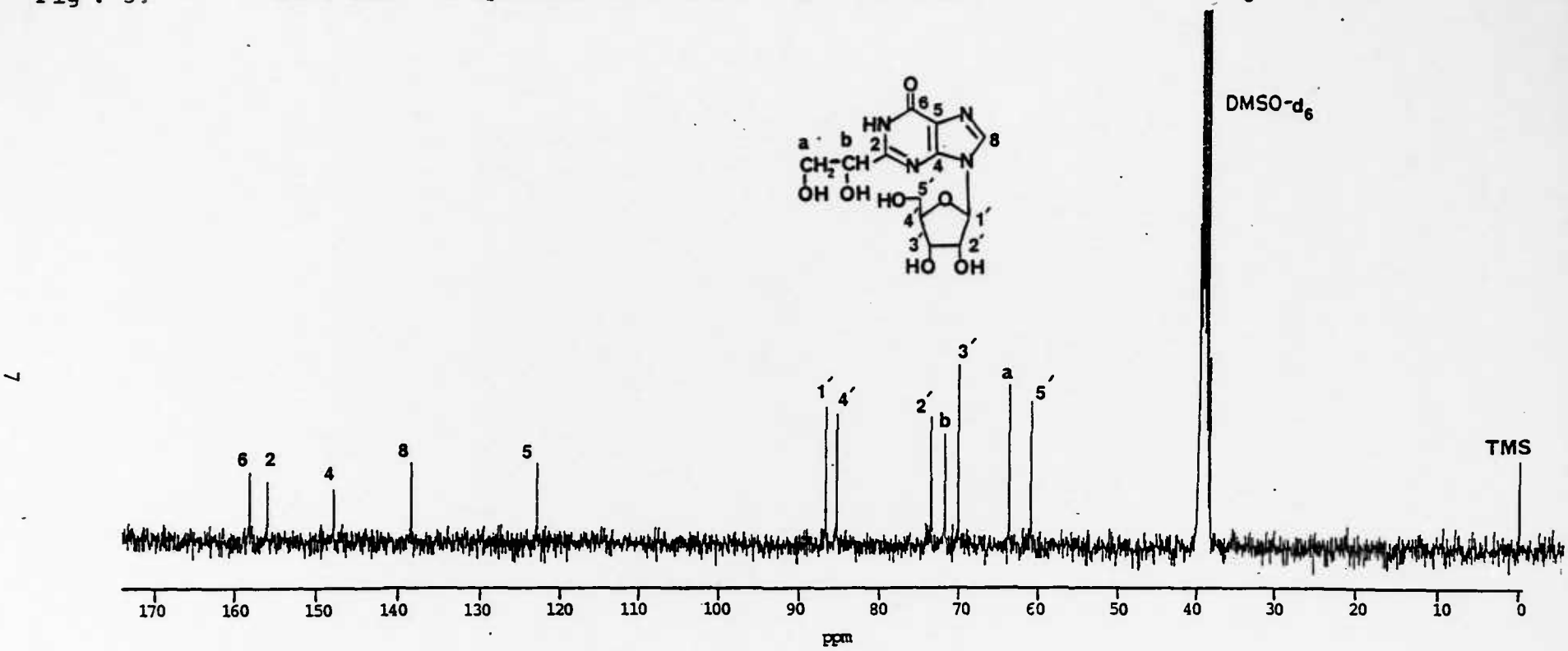
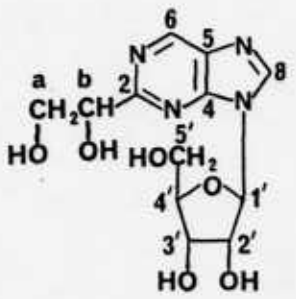
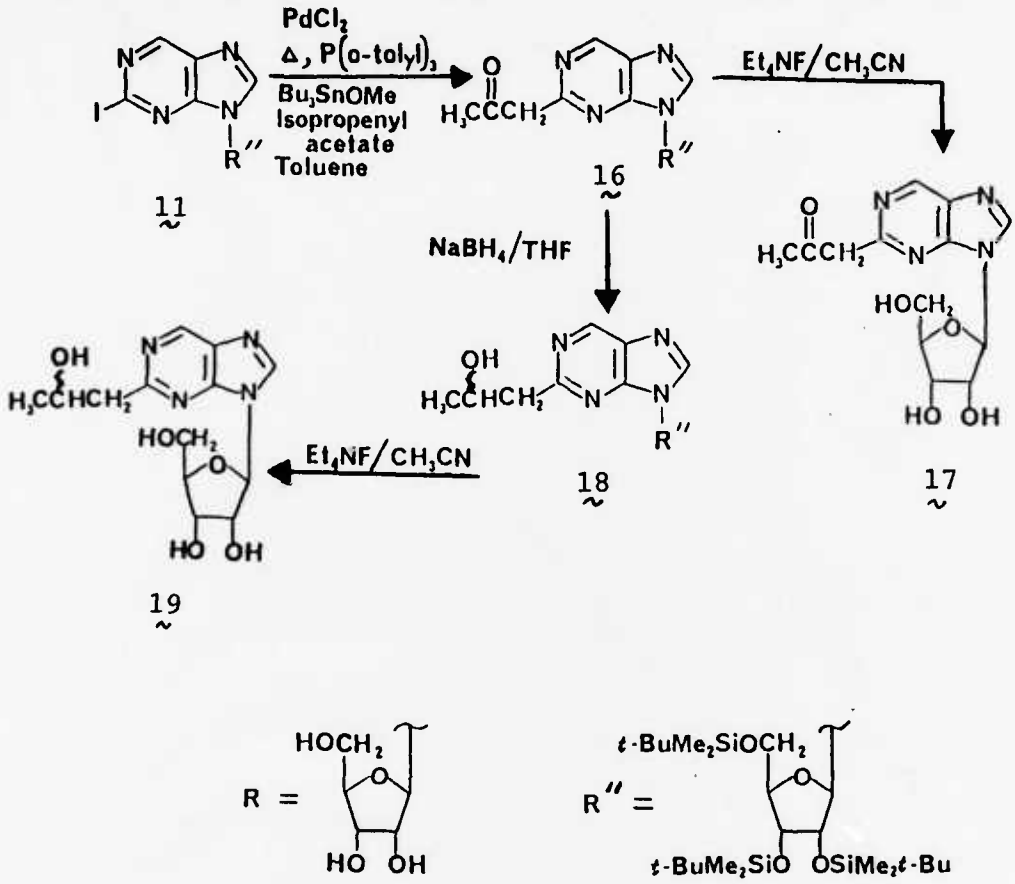


Fig. 4. 90.6 MHz ^{13}C NMR of 2-(1,2-Dihydroxyethyl)nebularine in DMSO-d_6



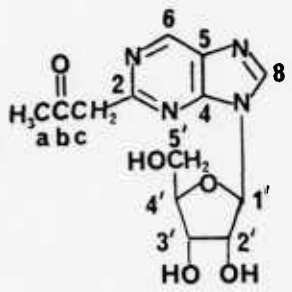
product 16 was obtained. Compound 16 was deprotected to the target molecule 17 with tetraethylammonium fluoride. The overall yield starting from guanosine was 6.0%. Reduction of the carbonyl functionality in 16 with sodium borohydride gave 18 in about 30% yield (Scheme 6). The reduction reaction proceeded sluggishly and considerable decomposition of the starting material occurred in this step. Deprotection of 18 gave the target diastereoisomeric alcohols 19. The ketone 17 and the alcohols 19 were purified by HPLC (Amberlite XAD-4 resin) and fully characterized. The ^{13}C NMR spectra of 17 and 19 are shown in Figs. 5 and 6.



Scheme 6

Access to the rare functionalized inosine analogue, 2-(2-hydroxyethyl) inosine 22, was made possible through the availability of the 2-vinyl compound 8. This compound was first protected by silylation to give 20, which was then treated with 9-borabicyclo[3.3.1]nonane (9-BBN). Oxidative work-up of the resulting organoborane gave the alcohol 21 in 52% yield. It should be mentioned that hydroboration reactions have rarely been used to elaborate structures in nucleoside chemistry. The above mentioned reaction was regiospecific and only one isomer was isolated. Deprotection of 21 with trimethylsilyl iodide in acetonitrile followed by treatment with

Fig. 5. 90.6 MHz ^{13}C NMR of 2-Acetonylnebularine in DMSO-d_6



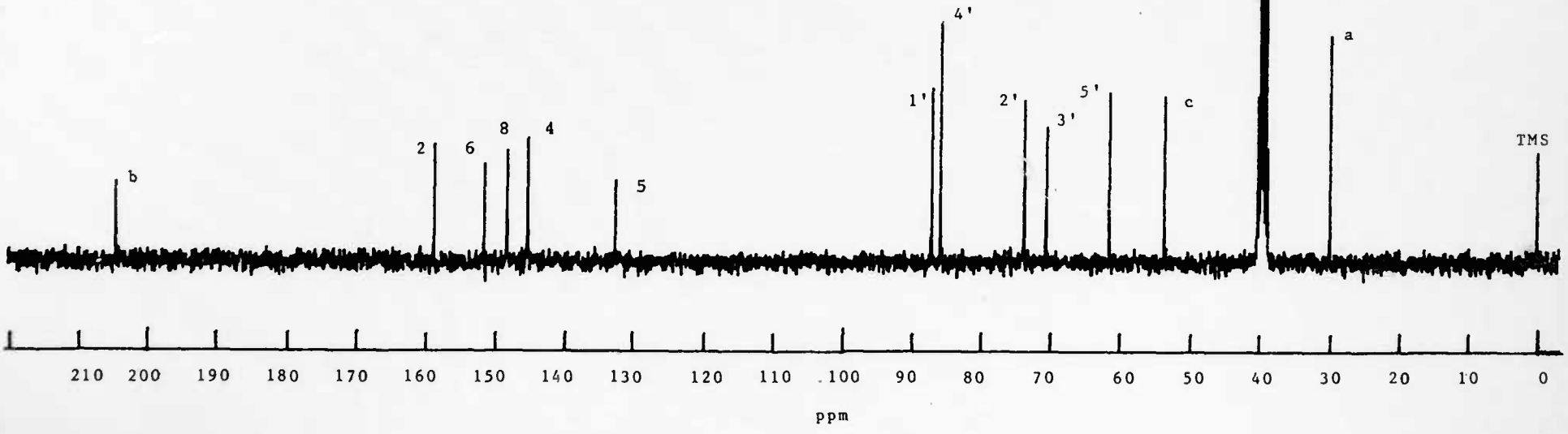
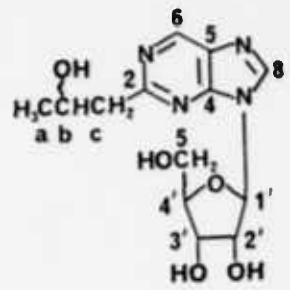
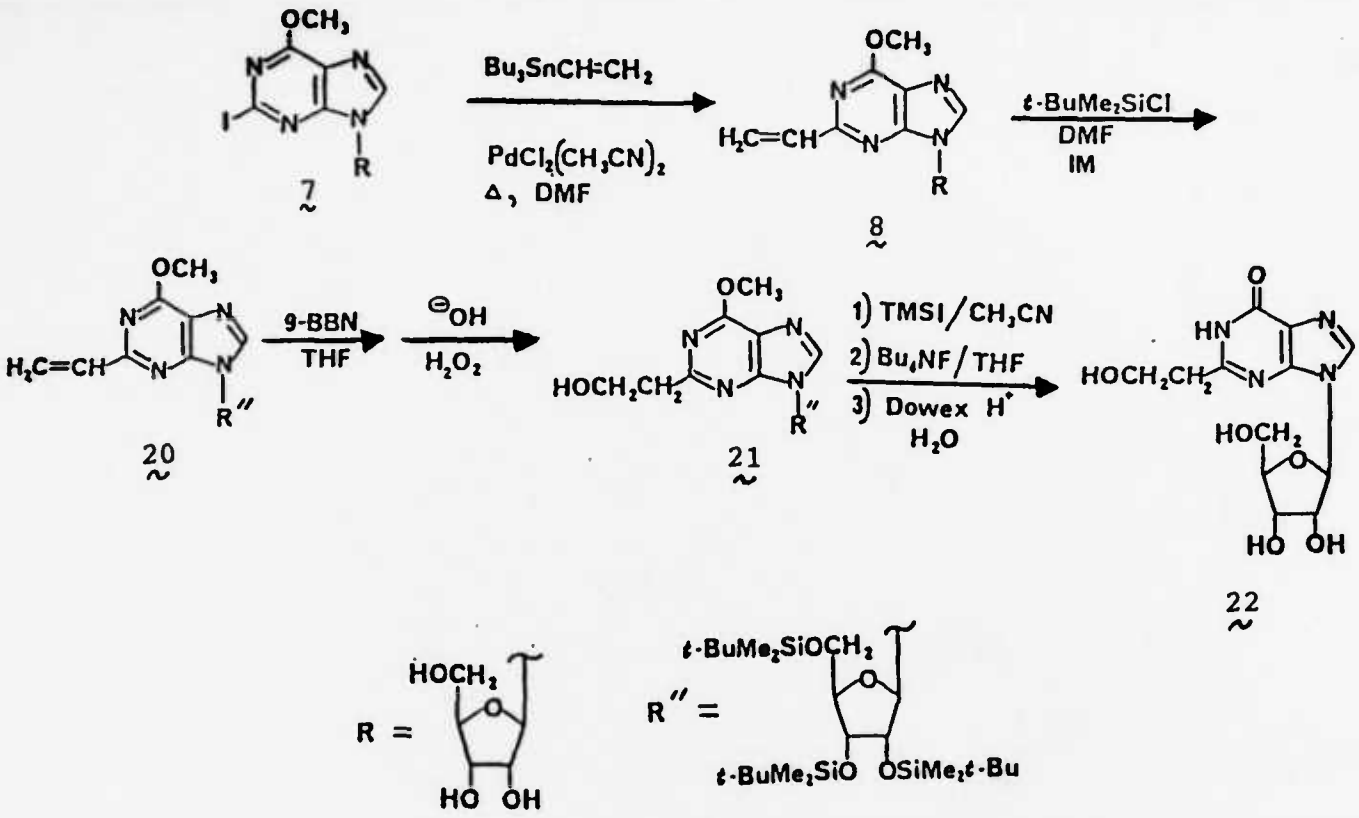


Fig. 6. 90.6 MHz ^{13}C NMR of 2-(2-hydroxypropyl)nebularine in DMSO-d_6

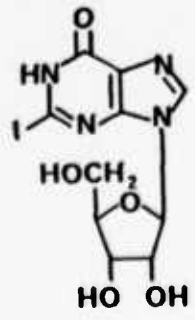


fluoride ions gave the target alcohol 22 (Scheme 7). Purification and characterization were carried out as described for other target compounds. The high-field ^{13}C NMR spectrum of 22 is enclosed (Fig. 7).

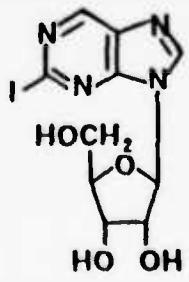


Scheme 7

In the last part of the second year of support, four compounds were submitted for antiviral evaluation. Two of the compounds, 23 and 24, were prepared by deprotection of key halogenated intermediates used in the syntheses previously described in this report. The other two compounds were target ketones 25 and 26 in which special emphasis was placed because of the potent antiviral activity of another ketone, 2-acetonylinosine, previously synthesized by us in this program.

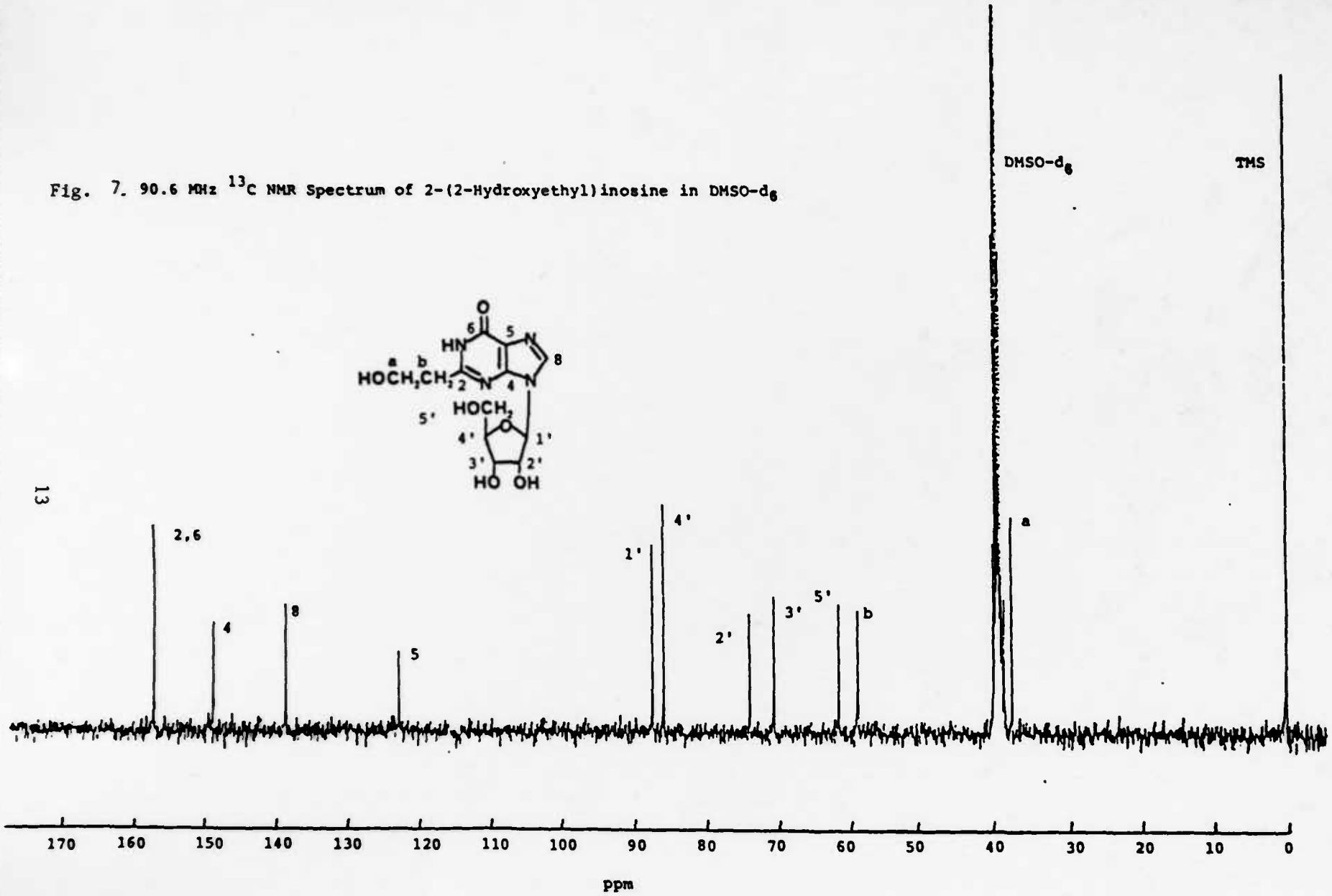


23

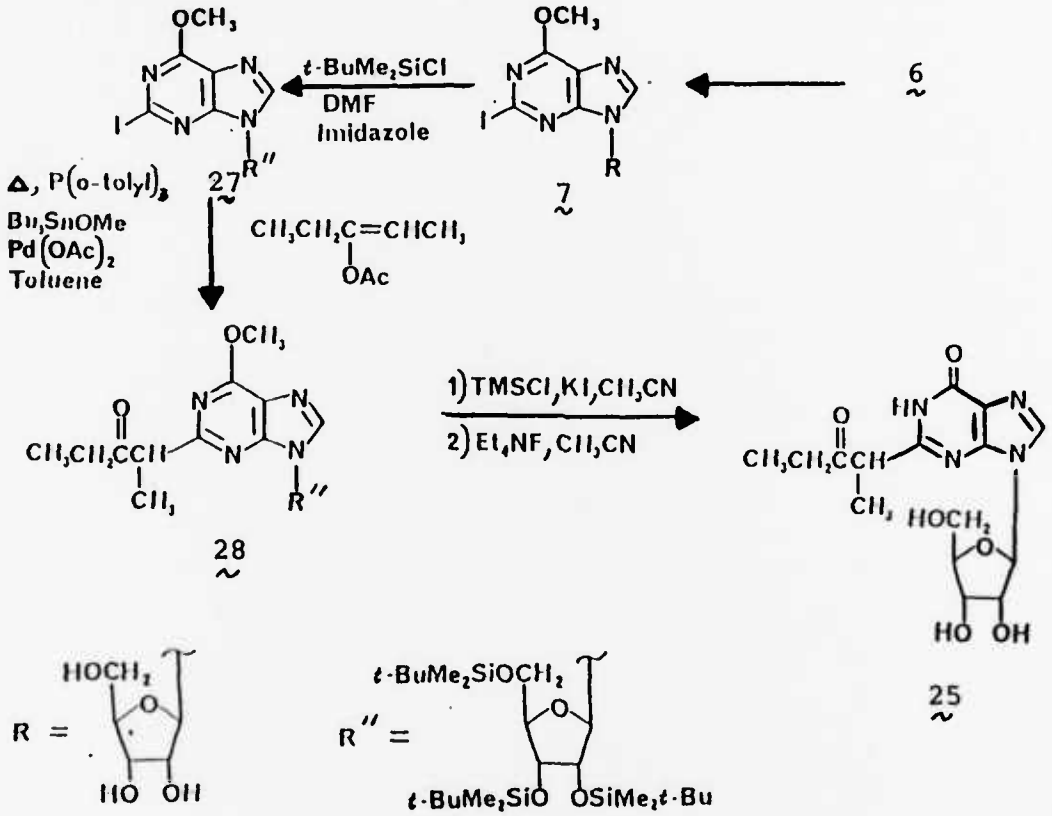


24

Fig. 7. 90.6 MHz ^{13}C NMR Spectrum of 2-(2-Hydroxyethyl)inosine in DMSO-d_6



The immediate precursor for the synthesis of the 2-ketoinosine 25 was the silylated 2-iodo compound 27, prepared from 2-iodo-6-methoxypurine nucleoside 7 (see synthesis of 7 in Scheme 2). When compound 27 was heated under reflux in toluene with palladium acetate, tri-o-tolylphosphine, tri-n-butyltin methoxide, and 2-pentene-3-acetate, very good yields of the keto compound 28 was isolated. The latter was deprotected to the target molecule 25 in two steps, first by reaction with trimethylsilyl iodide and then with tetraethylammonium fluoride (Scheme 8). Target compound 25 was purified by reversed-phase HPLC. The overall yield of 25 starting from guanosine was 10.8 %. It was fully characterized by spectral methods and by high-resolution fast atom bombardment mass spectrometry (FAB HRMS). The high-field ^{13}C NMR spectrum is shown in Fig. 8.



Scheme 8

Synthesis of the ketonebularine 26 was achieved using the silylated 2-iodopurine nucleoside 11 as the immediate precursor. Compound 11 can be prepared in six steps from guanosine as previously presented in Scheme 3. The palladium-catalyzed cross-coupling reaction of 11 to give 29 was carried out as described above for the conversion of 27 to 28. Excellent yields of product were obtained in this conversion. Deprotection of 29 (tetraethylammonium fluoride) followed by purification of the resulting material by HPLC, gave target molecule 26 (13.7% overall yield from guanosine). Compound 26 was fully characterized. The high-field ^{13}C NMR spectrum of 26 is shown in Fig. 9.

Fig. 8. 90.6 MHz ^{13}C NMR of 2-(1-Methyl-2-oxobutyl)-9-(β-D-ribofuranosyl)hypoxanthine in DMSO-d_6

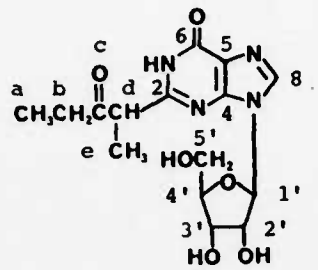
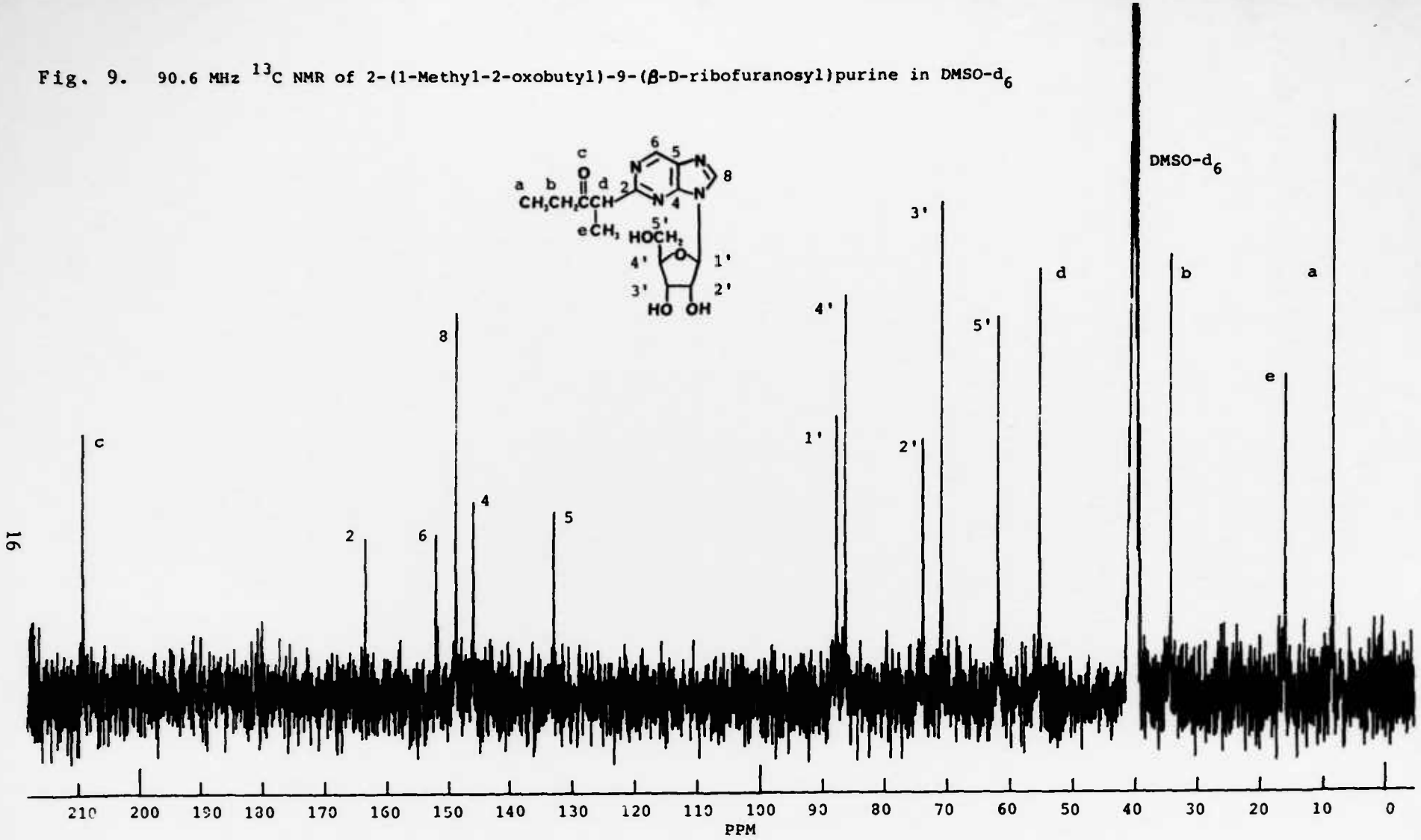
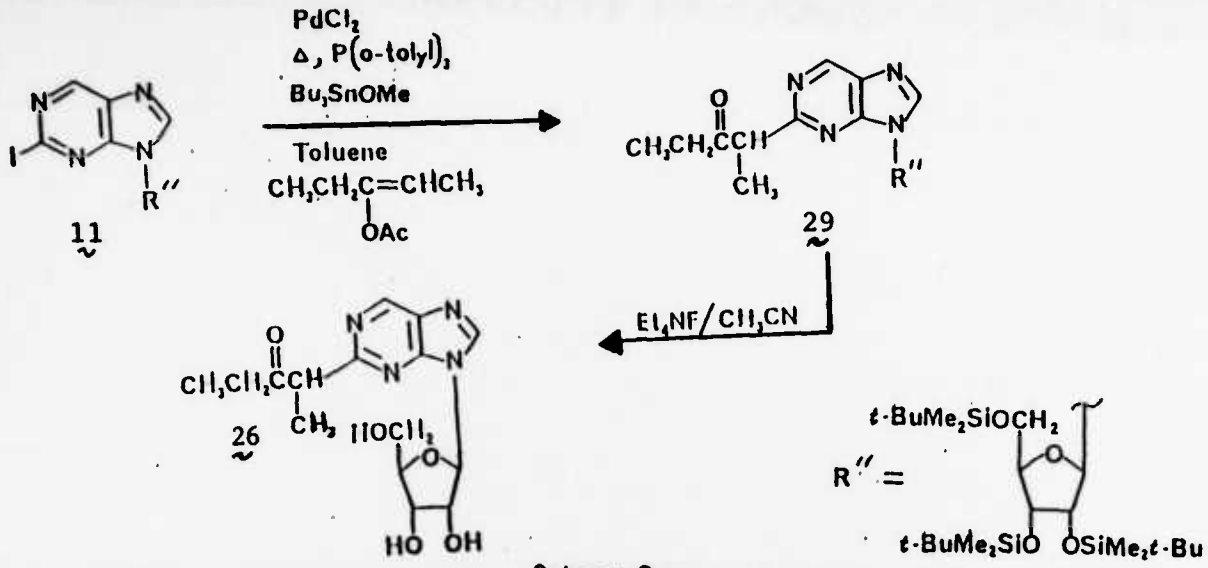


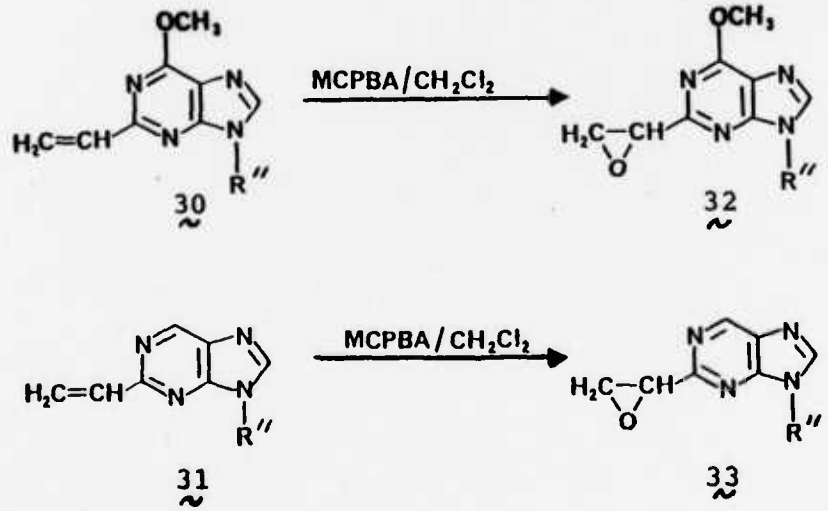
Fig. 9. 90.6 MHz ^{13}C NMR of 2-(1-Methyl-2-oxobutyl)-9-(β-D-ribofuranosyl)purine in DMSO-d_6





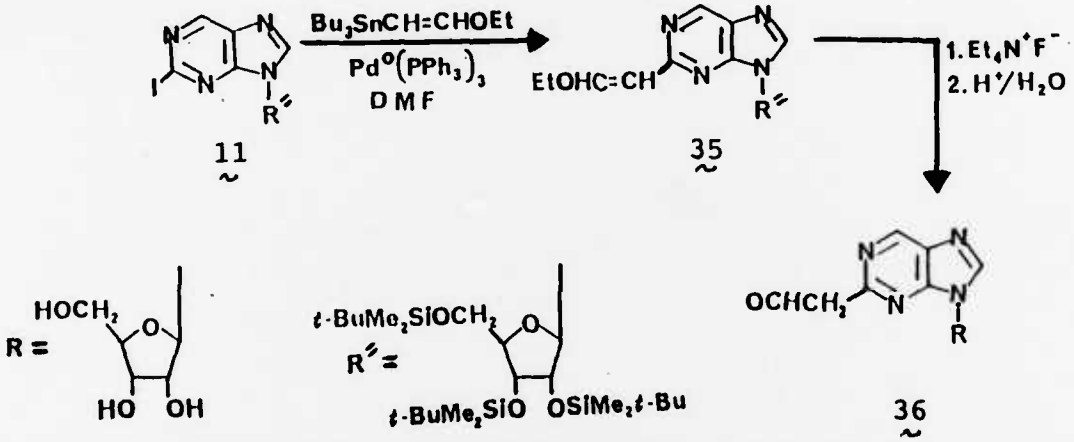
Scheme 9

Epoxy substituted purine nucleosides are very rare compounds and only one example of a purine system with an epoxy group at the 6-position is known (Nair and Chamberlain, J. Am. Chem. Soc. 1985, 107, 2183). The approach to the 2-epoxy compounds of the inosine and nebularine series was through the corresponding vinyl compound precursors (30 and 31) whose synthesis have been described previously in this report. Although epoxidation of these vinyl compounds appeared to have proceeded as expected to give the epoxides 32 and 33 (Scheme 10), isolation of the epoxide products was extremely difficult because of their inherent instability. Several different procedures for isolation and deprotection were attempted, but all were unsuccessful.



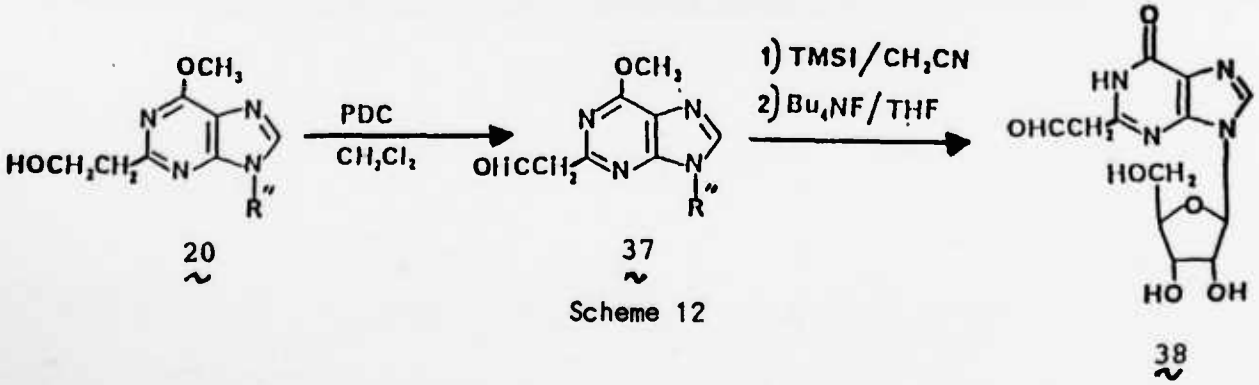
Scheme 10

During this second year of the contract, we have also been involved in the development of approaches to the synthesis of analogues of nebularine and inosine that contain aldehyde functionalized carbon-carbon bonding at the 2-position. The initial approach for the nebularine series was to synthesize the 2-(2-hydroxyethyl)purine system and selectively oxidize this primary hydroxyl group to the aldehyde. Although the synthetic procedure for the preparation of the 2-hydroxyethyl derivative of inosine had previously been developed by us, application of this (i.e. hydroboration followed by oxidative work-up) resulted in the formation of the 2-ethyl compound through reduction of the intermediate organoborane. An alternative procedure involved direct introduction of a masked aldehyde moiety at the C-2 position. This was achieved through the use of ethyl vinyltributyltin ether 34. The organostannane 34 was prepared by the radical coupling of tributyltin hydride with ethyl ethynyl ether. Palladium-catalyzed coupling of the organostannane 34 with protected 2-iodopurine nucleoside 11 gave the (E)- and (Z)- mixture of the expected product 35 in about 70% yield (Scheme 11). We are currently working on the removal of the protecting groups from 35 which would give us the target molecule 36.



Scheme 11

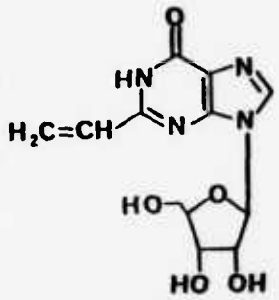
Synthesis of the protected aldehyde 37 through oxidation of 20 (a difficult reaction) was also successfully investigated. The deprotection step, which may pose some difficulties because of the sensitive nature of this aldehyde functionality, remains to be worked out (Scheme 12).



Scheme 12

6. List of Target Compounds and Intermediates Submitted:

(I) 2-Vinyl-9-(β-D-ribofuranosyl)hypoxanthine or 2-Vinylinosine

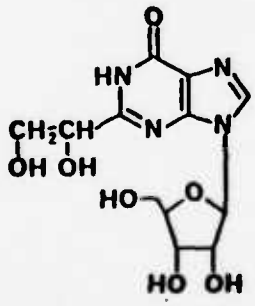


AVS Identifying No: AVS-002716
Contractor's Identifying Code No: VN-1-103
Report Reference: This Annual Report, Scheme 2

(II) 2-Vinyl-9-(β-D-ribofuranosyl)purine or 2-Vinylnebularine

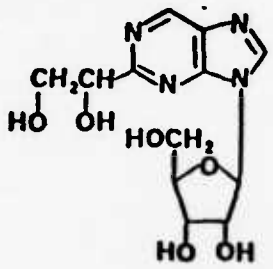
AVS Identifying No: AVS-002694
Contractor's Identifying Code No: VN-1-104
Report Reference: This Annual Report, Scheme 3

(III) 2-(1,2-Dihydroxyethyl)-9-(β-D-ribofuranosyl)hypoxanthine or 2-(1,2-Dihydroxyethyl)inosine



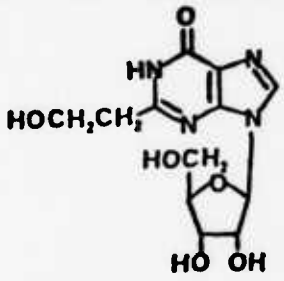
AVS Identifying No: AVS-002695
Contractor's Identifying Code No: VN-1-105
Report Reference: This Annual Report, Scheme 4

(iv) 2-(1,2-Dihydroxyethyl)-9-(β-D-ribofuranosyl)purine or 2-(1,2-Dihydroxyethyl)nebularine



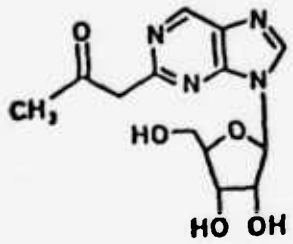
AVS Identifying No: AVS-002883
Contractor's Identifying Code No: VN-1-106
Report Reference: This Annual Report, Scheme 5

(v) 2-(2-Hydroxyethyl)-9-(β-D-ribofuranosyl)hypoxanthine or 2-(2-Hydroxyethyl)inosine



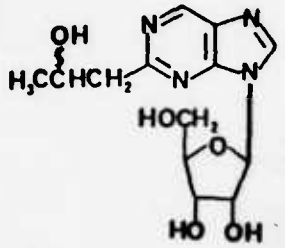
AVS Identifying No: AVS-002884
Contractor's Identifying Code No: VN-1-107
Report Reference: This Annual Report, Scheme 7

(vi) 2-Acetonyl-9-(β-D-ribofuranosyl)purine or 2-Acetonylnebularine



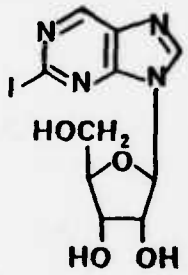
AVS Identifying No: AVS-003039
Contractor's Identifying Code No: VN-1-108
Report Reference: This Annual Report, Scheme 6

(vii) 2-(2-Hydroxypropyl)-9-(β-D-ribofuranosyl)purine or 2-(2-Hydroxypropyl)nebularine



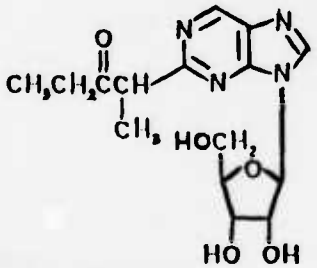
AVS Identifying No: AVS-003582
Contractor's Identifying Code No: VN-I-109
Report Reference: This Report, Scheme 6

(viii) 2-Iodo-9-(β-D-ribofuranosyl)purine or 2-Iodonebularine (Intermediate)



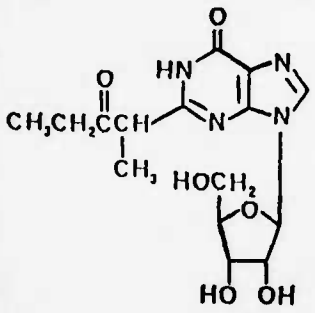
AVS Identifying No: AVS-003923
Contractor's Identifying Code No: VN-I-110
Report Reference: This Annual Report, Scheme 3

(ix) 2-(1-Methyl-2-oxobutyl)-9-(β-D-ribofuranosyl)purine



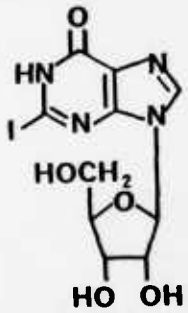
AVS Identifying No: AVS-003924
Contractor's Identifying Code No: VN-I-111
Report Reference: This Annual Report, Scheme 9

(x) 2-(1-Methyl-2-oxobutyl)-9-(β-D-ribofuranosyl)hypoxanthine



AVS Identifying No: AVS-003921
Contractor's Identifying Code No: VN-I-112
Report Reference: This Annual Report, Scheme 8

(xi) 2-Iodo-9-(β-D-ribofuranosyl)hypoxanthine or 2-Iodoinosine



AVS Identifying No: AVS-003922
Contractor's Identifying Code No: VN-I-113
Report Reference: This Annual Report, Scheme 2

7. Antiviral Screening Data:

AVS Identifying Number Contractor's Code Number	Antiviral Drug Screening Data
AVS-002159 VN-1-101	Very active, specific TI >1000 (in vitro, SF) HIV results not available Toxic in CCHF suckling mouse
AVS-002352 VN-1-102	Some activity against YF Not active against VSV, AD2, VV, HIV, SF, JE in vitro in vivo data not available
AVS-002716 VN-1-103	Some broad spectrum activity (in vitro) against YF, JE, AD2, VV, PT, RVF, not active against VEE, VSV, HIV in vivo data not available
AVS-002694 VN-1-104	Not active (in vitro) in vivo data not available
AVS-002695 VN-1-105	Not active (in vitro) in vivo data not available
AVS-002883 VN-1-106	Some activity against RVF Not active (in vitro) against other viruses HIV results not available in vivo data not available
AVS-002884 VN-1-107	Some activity against RVF Not active (in vitro) against other viruses HIV results not available in vivo data not available
AVS-003039 VN-1-108	Not active against AD2, JE, VSV, VV, RVF
AVS-003582 VN-1-109	Screening data not available
AVS-003923 VN-1-110	Screening data not available
AVS-003924 VN-1-111	Screening data not available

AVS-003921 VN-I-112	Screening data not available
AVS-003922 VN-I-113	Screening data not available

8. Bibliography of Publications, Patents, and Presentations:

(i) V. Nair, D. A. Young, and R. DeSilvia, Jr., 2-Halogenated Purine Nucleosides: Synthesis and Reactivity, Journal of Organic Chemistry, **1987**, 52, 1344 (4 copies furnished to SGRD-RMS).

(ii) V. Nair, D. A. Young, and R. DeSilvia, Jr., 2-Amino-9-(β-D-ribofuranosyl)purine. Photoinduced Reductive Dehalogenation: A General Approach to 2-Aminopurine and Related Systems, An Invited Article in "Nucleic Acid Chemistry", Part 4, Edited by L. B. Townsend and R. S. Tipson, 1987 (4 copies furnished to SGRD-RMS).

(iii) V. Nair, S. D. Chamberlain, R. DeSilvia, Jr., and G. S. Buenger, Synthetic Approaches to Rare 2-Substituted Purine Nucleosides, Nucleosides and Nucleotides, **1987**, 6, 229 (4 copies furnished to SGRD-RMS).

(iv) V. Nair and D. A. Young, Conformational Correlation of Purine Nucleosides by High-Field Carbon-13 NMR Data, Magnetic Resonance in Chemistry, **1987**, 25, 937 (4 copies furnished to SGRD-RMS).

(v) V. Nair, G. A. Turner, and S. D. Chamberlain, Novel Approaches to Functionalized Nucleosides via Palladium-Catalyzed Cross-Coupling with Organostannanes, Journal of the American Chemical Society, **1987**, 109, 7223 (4 copies furnished to SGRD-RMS).

(vi) V. Nair, Alkylated Inosines as Antiviral Agents, Patent Serial Number 67,498 filed with U. S. Patent Office, June 1987.

(vii) V. Nair, D. A. Young, S. D. Chamberlain, and G. S. Buenger, 2-Aminopurine Nucleosides: Synthesis, Biological Activity, and Reactivity, 21st Midwest Regional Meeting of the American Chemical Society, Kansas City, Missouri, November, 1986.

(viii) V. Nair, G. A. Turner, G. S. Buenger, and A. G. Lyons, Synthetic Approaches to New, Biologically-Active Purine Nucleosides, 194th National Meeting of the American Chemical Society, New Orleans, Louisiana, September, 1987.

(ix) V. Nair and G. S. Buenger, Novel 2-Substituted Purine Nucleosides, 99th Session of the Iowa Academy of Science, Grinnell, Iowa, April 1987.

(x) V. Nair and A. G. Lyons, Functionalization of Inosine, 99th Session of the Iowa Academy of Science, Grinnell, Iowa, April, 1987.

(xi) V. Nair, Rare 2-Substituted Purine Nucleosides, USAMRIID Department of Antiviral Studies Program Review, August, 1987.

(xii) V. Nair, Eight Invited Research Seminars on "The Search for New Antiviral Compounds: Rare 2-Substituted Purine Nucleosides", presented at major Universities in Sydney, Melbourne, and Adelaide, Australia, July, 1987, as part of an Award as Distinguished Visiting Professor/Scholar.

9. Personnel Supported:

Gregory A. Turner, Graduate Student, Ph.D. Degree, May 1987
Greg S. Buenger, Graduate Student
Arthur G. Lyons, Graduate Student
Brian J. Hettrick, Graduate Student

10. Summary:

In the second year of this contract, we have had considerable success in our synthetic work and a total of eleven rare 2-substituted purine nucleosides (nine target compounds and two intermediates) were synthesized, purified, characterized, and submitted to the Department of Antiviral Studies. Our progress on this contract is now right on schedule. Although screening data are not available as yet on several of the compounds submitted, some very interesting and positive data have been received. One compound (2-acetonylinosine, AVS-002159) has been found to have very high activity (TI > 1000) against the Sandfly Fever Virus (Phlebovirus). Another compound (2-vinylinosine, AVS-002716) has been found to have low but broad spectrum activity against a number of RNA viruses. Two other compounds (AVS-002883 and AVS-002884) have shown some activity against the Rift Valley Fever Virus, and still another (AVS-002352) has shown activity against the Yellow Fever Virus. Five publications have appeared in 1987 on this work. In addition, a patent has been filed on some of the inosine analogues synthesized. Various aspects of the synthetic work have also been presented as invited and contributed papers and research seminars at regional, national, and international scientific meetings and occasions.